

BIOPESTICIDES REGISTRATION ACTION DOCUMENT

Linalool
(3,7-Dimethyl-1,6-octadien-3-ol)

(PC Code 128838)

U.S. Environmental Protection Agency

Office of Pesticide Programs

Biopesticides and Pollution Prevention Division

Prepared by Stephen Morrill

BIOPESTICIDES REGISTRATION ACTION DOCUMENT TEAM

Office of Pesticide Programs:

Biopesticides and Pollution Prevention Division

Steve Morrill	Special Assistant
Linda Hollis	BPB Branch Chief
Todd Petersen, Ph.D.	Biologist, Regulatory Action Leader
Russell Jones, Ph.D.	Senior Scientist
Roger Gardner	Senior Scientist
Angela Gonzales	Biologist
Dwight Welch	Product Chemist

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I. EXECUTIVE SUMMARY

Active Ingredient and Mode of Action

Linalool (3,7-dimethyl-1,6-octadien-3-ol) is a terpenoid alcohol found naturally in a variety of plants, flowers and spices. As a pesticide, Linalool is intended for use indoors to control pests (fleas and ticks) on pets and the spaces they inhabit by affecting the insect's nervous system. Linalool is also used as an outdoor mosquito inhibitor. Because of its flavorful and fragrant properties, Linalool has non-pesticide uses and it is added to processed food and beverages, perfumes, cosmetics and soaps as well as to household detergents and waxes. The Food and Drug Administration considers Linalool to be generally recognized as safe (GRAS) as a synthetic flavoring substance and adjuvant in food for human consumption (21 CFR 182.60) and as an ingredient in animal drugs, feeds and related products (21 CFR 582.60).

Toxicology Assessment

The toxicological studies discussed in the Human Health Assessment below were evaluated and found to support the unconditional registration of this active ingredient for the currently registered sites. These data also meet the safety standards examined under Registration Review mandated by the amended Food Quality Protection Act (FQPA) of 1996.

Tier I Data submitted to support the initial registration of the active ingredient Linalool include acute toxicity to demonstrate oral, inhalation, dermal exposure, eye irritation, dermal irritation and skin sensitization. The active ingredient is classified as follows: toxicity category III for acute oral, dermal exposure and eye irritation and toxicity category IV for acute inhalation and dermal irritation. Linalool is not a sensitizer. Subchronic, developmental, mutagenicity, and immunotoxicity data were submitted or cited and found to be acceptable. Tier I acute toxicology data submissions and information did not trigger endpoints requiring Tier II or Tier III data requirements. No further toxicology data are required for the current uses of Linalool. Additional data requirements for other proposed uses will be considered on a case-by-case basis.

Food Tolerances

No tolerances have been established or proposed for Linalool as there are no current or proposed food uses for pesticide products containing Linalool. Exposure to the active ingredient is solely limited to residential use.

FQPA Considerations

Not applicable since there are no current or proposed food uses for pesticide products containing Linalool.

Occupational and Residential Exposure and Risk

The Agency conducted an occupational, residential and day care exposure assessment for all end use products containing Linalool. Based on the use patterns of products containing

linalool as an active ingredient, anticipated exposure is not likely to result in unreasonable risk to humans or the environment.

Ecological and Environmental Exposure and Risks

The submitted ecological and environmental exposure studies and accompanying waiver requests and justifications fulfill the respective OPPTS data requirements for the ecological assessment of Linalool and are considered acceptable. Ecological testing was not required for indoor uses of Linalool and guideline data requirements were waived for outdoor uses since there is no direct exposure to non-target organisms.

In the unlikely event that some non-target organisms are affected during the commercial application of this product, such incidents should immediately be reported to the EPA, as required under FIFRA Section 6(a)(2), so that the Agency may take appropriate action.

Environmental Justice

The Agency does not believe that the use of Linalool will result in environmental justice related issues and does not, therefore, require special consideration under Executive Order 12898, entitled Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations (59 FR 7629, February 16, 1994).

Endangered Species Considerations

Linalool is intended for use indoors to control pests on pets and the spaces they inhabit and as an outdoor insect inhibitor. There is no exposure to non-target organisms resulting from strictly indoor uses. Outdoor exposure may occur when pets treated with Linalool-containing shampoos are permitted to be outdoors or through the use of the candle and the fragrance generator products. Linalool is rapidly diluted by the atmosphere as it diffuses away from its point sources in fragrance generators and candles, and on animals (as a component of pet treatment products).

Due to the volatility of Linalool and its rapid dilution in the atmosphere, outdoor uses preclude any residue accumulation in terrestrial and aquatic environments. Outdoor uses of Linalool only affect (inhibit) biting insects; other non-target insects are unaffected.

Based on its assessment, EPA has determined that there will be No Effects (NE) of Linalool on threatened and endangered species when products containing this active ingredient are used in accordance with approved labeling.

Data Gaps and Requirements/Labeling

There are no data deficiencies for Linalool. However, if more extensive use patterns are sought, or if other methods of application are requested, additional information and data will be required on a case-by-case basis.

II. OVERVIEW

A. Product Overview:

- | | |
|--------------------------------|----------------------------------------------|
| 1. Biological Name: | Linalool (3,7-dimethyl-1,6-octadien-3-ol) |
| 2. Trade/Other Names: | Technical Linalool |
| 3. OPP Chemical Code: | 128838 |
| 4. Basic Manufacturers: | Wellmark International
Bedoukian Research |

B. Use Profile:

- | | |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Type of Pesticide: | Insecticide, Repellent/Inhibitor |
| 2. Use Sites: | Linalool is applied to indoor residential carpets as a surface spray or powder and to dogs and cats as a spray, dip, shampoo or mousse. It is also used outdoors in a scent generator and as scented candles to inhibit mosquitoes. |
| 3. Target Pests: | Linalool is used control fleas, mites, spiders, ticks and to inhibit mosquitoes. |
| 4. Formulation Types: | Liquid (sprays, dips, shampoos, concentrated fragrance) powder, fogger, and solid (candle). |
| 5. Application Method: | <i>Pets:</i> Applied directly to pets as an aerosol and non-aerosol spray, powder, dip and mousse as needed.
<i>Indoor Residential:</i> Applied directly to carpets as a directed spray powder or as a space spray or fogger as needed.
<i>Outdoor Residential Mosquito Inhibitor:</i> Applied as a scented candle or a scent generator as needed. |

C. Estimated Usage: Manufacture and sales of the pesticide have been reported to the Agency and are a matter of Confidential Business Information.

D. Data Requirements: Data and accompanying information, submitted under section 3(c)(5) of FIFRA in support of this unconditional registration, were reviewed by BPPD. Product

identity and analysis data, as well as documents submitted for acute mammalian toxicity and ecological effects, meet the requirements set forth for the labeled use patterns. If label instructions are followed, the Agency foresees no unreasonable adverse affects to human health and the environment from use of Linalool.

E. Regulatory History:

1. Food Additive History: In 1965, Linalool was approved as a direct food additive and is considered to be generally recognized as safe (GRAS) by the FDA as a synthetic flavoring substance and adjuvant in food for human consumption (21 CFR 182.60) and as an ingredient in animal drugs, feeds and related products (21 CFR 582.60). According to the Joint FAO/WHO Expert Committee on Food Additives, an average daily intake (ADI) for Linalool was set at 0 to 0.5 mg/kg body weight (2003).

2. Product Registration History: Currently, there are 16 registered products containing Linalool as an active ingredient. Of these products, five contain Linalool as the only active ingredient, two of which are Manufacturing-Use Products (MUPs). Two of the three remaining products are used as mosquito inhibitors in outdoor and semi-enclosed spaces, and the last product is used as a pet flea shampoo.

The 11 remaining products contain Linalool in combination with other active ingredients. Five products are pet sprays, dips, or shampoos, five products are carpet and surface treatments, and the last product is a fogger for use indoors.

Technical MUPs

Technical Linalool / EPA Reg. Number 4758-150: Registered on March 15, 1985 by Pet Chemicals and transferred to Wellmark International on March 23, 2006 and issued new EPS Reg. Number 2724-762.

Mosquito-L / EPA Reg. Number 52991-13: Registered on January 10, 2000 by Bedoukian Research Inc.

Linalool Only Products

Holiday Concentrated Dog and Cat Shampoo / EPA Reg. Number 4758-155: Registered on October 3, 1985 by Pet Chemicals and transferred to Wellmark International on March 3, 2006 / EPA Reg. No. 2724-766.

Mosquito Cognito / EPA Reg. Number 70909-2: Registered on December 21, 2004 by BioSensory Inc.

Conceal Candle / EPA Reg. Number 70709-5: Registered on December 21, 2004 by BioSensory Inc.

*Linalool Products
Containing
Multiple A.I.s.*

Holiday Pet Spray / EPA Reg. Number 2724-618: Registered on November 11, 1993 by Wellmark International.

Hill's Holiday Flea Stop for Dogs and Cats / EPA Reg. Number 4758-151: Registered on October 1, 1985 by Pet Products and transferred to Wellmark International on March 6, 1985 / EPA Reg. No. 2724-763.

Holiday Non-Aerosol Fleas Spray / EPA Reg. Number 4758-153: Registered by Pet Products on May 16, 1997 and transferred to Wellmark International on March 26, 2006 / EPA Reg. Number 2724-784

Demize E.C. / EPA Reg. Number 4758-161: Registered by Pet Products on November 29, 1986 and transferred to Wellmark International on March 23, 2006 / EPA Reg. Number 2724-769

Flea Stop Lunatic Dip / EPA Reg. Number 2724-770: Registered by Wellmark International on July 7, 1996.

Permalool Home and Carpet Spray / EPA Reg. Number 4758-164: Registered by Pet Products on September 19, 1998 and transferred to Wellmark International on March 3, 2006 / EPA Reg. No. 2724-771

Permalool Plus Fogger / EPA Reg. Number / 4758-165: Registered by Pet Products on January 3, 2003 and transferred to Wellmark International on March 16, 2006 / EPA Reg. No. 2724-772

Pemalool Plus Home and Carpet Spray / EPA Reg. Number 4758-166: Registered by Pet Products on July 12, 2004 and transferred to Wellmark International on March 6, 2006 / EPA Reg. No. 2724-773.

Permalool Plus Inverted Carpet Spray / EPA Reg. Number 4758-169: Registered by Pet Products on May 15, 2003 and transferred to Wellmark International on March 16, 2006 / EPA Reg. No. 2724-774

Linalool Mousse / EPA Reg. Number 4758-171: Registered by Pet Chemicals on May 1, 2003 and transferred to Wellmark International on 3/6/06 / EPA Reg. No. 2724-776.

Linalool Plus Carpet Powder / EPA Reg. Number 4758-172: Registered by Pet Chemicals on September 9, 2004 and transferred to Wellmark International on March 16, 2006 / 2724-777

F. Registration Review: This BRAD is being issued concurrently with EPA's Registration Review Decision for Linalool pursuant to 40 CFR Sections 155.57 and 155.58. A registration review decision is the Agency's determination that a pesticide meets, or does continue to meet the standard for registration in FIFRA.

The Agency's Final Decision is that no additional data are required at this time to support the continued registration of Linalool. The Agency considered Linalool in light of the standard for registration and safety factors in FIFRA and FFDCA as amended by FQPA. EPA has found that there are not likely to be any unreasonable adverse effects to the U.S. population in general, and to infants and children in particular, or to non-target organisms, from the use of products containing Linalool when currently required label instructions are followed.

III. RISK ASSESSMENT

A. Physical and Chemical Properties Assessment: The registrant submitted studies to satisfy Product Chemistry requirements for Technical Linalool. Information regarding product identity/composition and physical/chemical characteristics was reviewed by the Agency and found to be acceptable. The following table contains information summarized from the Biopesticides and Pollution Prevention Division (BPPD) Data Evaluation Record (DER) from Dwight A. Welch, dated January 11, 2008.

Table 1. Product Chemistry Data Requirements				
Data Requirement 40CFR Part 158.2030	Guideline #	MRID #	Classification	Finding
Product identity and Composition	880.1100	442501-017	Acceptable	Linalool (3,7-Dimethyl-1,6-octadien-3-ol) 94%
Description of starting materials, production and formulation process	880.1200	442501-017	Acceptable	An acceptable discussion was submitted.

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Discussion of formation of impurities	880.1400 158-2030	442501-017	Acceptable	Nominal concentration and certified limits were within acceptable levels.
Preliminary analysis	830.1700	442501-017	Acceptable	Product falls within certified limits.
Certification of limits	830.1750	442501-017	Acceptable	AI: 92.5% (min) – 95.0% (max); Nominal concentration and certified limits for the inerts were within acceptable levels.
Enforcement analytical method	830.1800	442501-017	Acceptable	An acceptable Gas Chromatography was submitted.
Color	830.6302*	442501-017	Acceptable	Colorless
Physical State	830.6303	442501-017	Acceptable	Liquid
Odor	830.6304	442501-017	Acceptable	Fresh floral-woody odor
Stability	830.6313	442501-017	Acceptable	Stable under normal use conditions
Flammability	830.6315	442501-017	Acceptable	174 degrees F
Storage stability	830.6317	442501-017	Acceptable	NR
Miscibility	830-6319	442501-017	Acceptable	NR; not emulsifiable and not diluted with petroleum solvents
Corrosion characteristics	830.6320	442501-017	Acceptable	Not corrosive
pH	830.7000	442501-017	Acceptable	Not Required, not soluble in water
Viscosity	8807100	442501-017	Acceptable	Not Required
Melting Point	880.7200	442501-017	Acceptable	Not Applicable
Boiling point/boiling range	830.7220	442501-017	Acceptable	379 degrees F

Density/relative density/bulk density	830.7300	442501-017	Acceptable	Approximately 0.86 g/ml at 25 degrees C
Partition coefficient (n-Octanol/Water)	830.7500 830.7560 830.7570	442501-017	Acceptable	N/A – polar compound
Water solubility	830-7840 158-2030	442501-017	Acceptable	Very slight (0.3g/100 ml)

B. Human Health Assessment:

1. Human Health Testing Requirements: As per 40CFR Part 158.2050, the registrant submitted or cited required human health studies to support registered uses of Linalool. Information summarized below and included in Table 2 was obtained from the Registration Division Precautionary Labeling Review Dated 10/15/84, Biopesticides and Pollution Prevention Division (BPPD) Data Evaluation Record (DER) from Russell S. Jones dated November 14, 1998, and BPPD Exposure Assessment from Angela Gonzales and Roger Gardner dated January 23, 2008.

a) Acute Toxicity (TIER I): The registrant submitted toxicity data (MRID #s 144120, 144121, 144122, 144123, 144124 & 145677). The active ingredient is classified as follows: toxicity category III for acute oral, dermal exposure and eye irritation and toxicity category IV for acute inhalation and dermal irritation. Linalool is not a sensitizer.

b) Subchronic Testing (TIER I): The following endpoints were selected from the Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS): **Oral:** An oral dose of 500 mg/kg Linalool was administered for 64 days. No toxicity effects were observed. The No Observable Effect Level (NOEL) was established at >500 mg/kg. **Dermal:** The NOEL was established at 250 mg/kg and the LOEL was established at 1000 mg/kg.

c) Reproductive and Developmental Toxicity (TIER I & II): The following endpoints were selected from the Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS): Parental: NOEL = 729 (highest dose tested). Offspring: NOAEL = 365 mg/kg; LOAEL = 729 mg/kg.

d) Mutagenicity Testing (TIER I): Reviews of mutagenicity testing reported negative results for five Ames assay studies and an unscheduled DNA synthesis study. Linalool was found not to be a mutagen. **TIER II Mutagenicity Testing** was not required.

e) Immunotoxicity Testing (TIER II): A study described by the OECD SIDS report indicated no suppression of the immune system by Linalool as measured by a plaque-forming cell (PFC) assay and by a host resistance assay.

f) Chronic Testing/Special Testing (TIER III): Not required.

2. Dose Response Assessment:

a) Endpoint Selection: Subchronic oral and reproduction toxicity studies demonstrate no effects in adult animals at doses ≥ 729 mg/kg body weight (a dose level approaching 1,000 mg/kg body weight as a limit dose) indicating low toxicity. In addition, in a subchronic dermal study a limit dose of 1,000 mg/kg, decreased weight gain, decreased activity and caused erythema. At a lower dermal dose of 250 mg/kg, erythema was observed, but no systemic effects were reported at that dose.

b) Effects on the Endocrine System: EPA is required under SECTION 408(P) of the Federal Food and Drug Administration (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide product active and other ingredients) “may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC’s recommendation that it include evaluations of potential effects in wildlife.

The Agency has no knowledge of Linalool being an endocrine disruptor. Consequently, endocrine-related concerns did not adversely impact the Agency’s safety finding for Linalool.

When the appropriate screening and/or testing protocols being considered under the Agency’s Endocrine Disruptor Screening Program (EDSP) have been developed and vetted, Linalool may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

Table 2. Human Health Assessment Data Requirements				
Data Requirement 40CFR Part 158.2050	Guideline #	MRID #	Classification	Finding
Acute Testing (TIER I)				
Acute Oral Toxicity	870.1100	144122	Acceptable	LD ₅₀ = 4.858 mg/kg Toxicity Category III
Acute Inhalation Toxicity	870.1300	144121	Acceptable	LC ₅₀ = 2.95 mg/L Toxicity Category IV
Acute Dermal Toxicity	870.1200	145677	Acceptable	LD ₅₀ = 2g/kg Toxicity Category III
Acute Eye Irritation	870.2400	144120	Acceptable	Moderate irritant Toxicity Category III
Acute Dermal Irritation	870.2500	144123	Acceptable	Slight irritant Toxicity Category IV
Skin Sensitization	870.2600	144124	Acceptable	Not a sensitizer
Subchronic Testing (TIER I)				
90-day oral	870.3100	445974-01	Acceptable	NOEL > 500 mg/kg
90-day dermal	870.3250	445974-01	Acceptable	NOEL > 250 mg/kg LOEL = 1000 mg/kg
90-day inhalation	870.3465	445974-01	Not Required	NA
Developmental Toxicity (TIER I)				
Prenatal Development	870.3700	NA	Not Required	NA
Mutagenicity (TIER I)				
In vivo Mammalian cell assay	870.5100 & 870.5300 & 870.5375	156098	Acceptable	Negative results for five Ames assay studies and an unscheduled DNA synthesis study. Not a mutagen
Mutagenicity (TIER II)				
In vivo Mammalian Cytogenetics	870.5385 & 870.5895	NA	NR	NA
Developmental Toxicity (TIER II)				
Prenatal developmental	870.3700	NA	Not Required	NA
Special Tests (TIER II)				
Immunotoxicity	880.3550	Public	Acceptable	No negative effects of

Table 2. Human Health Assessment Data Requirements				
Data Requirement 40CFR Part 158.2050	Guideline #	MRID #	Classification	Finding
		Literature		Linalool on the immune system.
Applicator/User Exposure (TIER II) *				
Dermal outdoor exposure	875.1100	NA	Not Required	NA
Dermal indoor exposure	875.1200	NA	Not Required	NA
Inhalation outdoor exposure	875.1300	NA	Not Required	NA
Inhalation indoor exposure	875.1400	NA	Not Required	NA
Biological monitoring	875.1500	NA	Not Required	NA
Chronic Testing/Special Testing (TIER III)				
Immune response	880.3800	NA	Not Required	NA
Reproduction and fertility effects	870.3800	Public Literature	Acceptable	Parental: NOAEL \geq 729 mg/kg Offspring: NOAEL = 365 mg/kg. LOAEL = 729 mg/kg
Chronic oral rodent and non-rodent	870.4100	NA	Not Required	NA
Carcinogenicity	870.4200	NA	Not Required	NA
Mammalian spermatogonial chromosome aberration test	870.5380	NA	Not Required	NA
Companion animal safety	870.7200	NA	Not Required	NA

* Although Applicator/User Exposure Guideline Studies were not required, EPA did conduct a residential exposure assessment for products containing Linalool and the results of that assessment are summarized below.

3. Dietary Exposure: The Agency did not conduct a dietary exposure risk assessment for Linalool. No tolerances have been established or proposed for Linalool as there are no current or proposed food uses for pesticide products containing Linalool. Exposure to the active ingredient is solely limited to residential use.

4. Drinking Water: In its initial risk assessment conducted in 1985, the Agency determined that there would be little or no exposure resulting from indoor uses of Linalool to drinking water.

The Agency determined that there would be no direct exposure to water from the mosquito inhibitor products as they are contained within a screened device or a candle. The Agency also determined that there would be no direct exposure to water for pet treatment products. For both pet treatment and mosquito inhibitor products, environmental exposure occurs via volatilization into the atmosphere. For the pet treatment products, exposure also occurs from direct contact with a pet treated with a Linalool-containing product. Linalool is rapidly diluted by the atmosphere as it diffuses away from its point sources in fragrance generators and candles, and on animals (as a component of a pet treatment product).

During the Registration Review of Linalool (see part II F above), comments were submitted to EPA by Tri-TAC, a California water treatment organization, who expressed concern about the water quality impacts of indoor residential pesticide uses (pet and surface treatments in the case of Linalool). Tri-TAC disagreed with the Agency's determination that there is no exposure of Linalool to non-target organisms and/or drinking water. Tri-TAC requested that EPA conduct an aquatic exposure, "Down the Drain Assessment," to evaluate the potential impact to aquatic organisms from indoor uses of Linalool.

In response to Tri-TAC comments, the Agency considered conducting an aquatic exposure, Down the Drain Assessment (DOA). However, the Agency determined that the use level of Linalool in pesticide products is so low that a DOA would not produce meaningful results. In light of its low usage and the fact that Linalool has been used as a food flavoring and fragrance since 1965, the Agency concluded that it is unlikely that registered Linalool pesticide products present a significant source of the Linalool found in Public Owned Treatment Works (POTW).

5. Occupational, Residential, School and Day Care Exposure: The Agency conducted an occupational, residential and day care exposure assessment for all end use products containing Linalool. Based on the use patterns of products containing Linalool as an active ingredient, anticipated exposure is not likely to result in unreasonable risk to humans or the environment. The following is information summarized from the Biopesticides and Pollution Prevention Division (BPPD) Data Evaluation Record (DER) from Angela Gonzales, dated January 23, 2008.

For the assessment, exposure scenarios included residential outdoor uses (mosquito repellents), pet treatments (application and post-application), indoor fogger use, and indoor carpet and surface area treatments. Post-application estimates included dermal and incidental oral exposures. Estimates of potential exposures were based exclusively on default assumptions which tend to exaggerate potential exposures when compared to previous Agency experience with pesticides having exposure data and being used in the same way as Linalool. These assumptions include 100% dermal absorption and the use of maximum transfer coefficients. An initial step in the analysis was to compare these estimates with the 0.5 mg/kg body weight average daily intake described by the FAO/WHO to identify use patterns that could result in significant risks not previously associated with the non-pesticide uses of Linalool. The analysis indicated that post-application exposures for children are most likely to exceed the defined level of concern. This approach limited the risk characterizations to exposures involving children; adults using linalool in most cases were not likely to be exposed to levels exceeding the average daily intake. No oral study evaluated a dose at which effects were seen in adult animals or at a similar level to the highest dose used in the repeated-dose dermal toxicity study (1000 mg/kg/day), and the 365 mg/kg/day NOAEL reported in offspring from the oral reproduction toxicity study was selected as the endpoint for risk characterizations in the assessment.

Risk characterizations are expressed as margins of exposure (MOE) defined by the ratio of the 365 mg/kg/day NOAEL from the reproduction toxicity study described above and the estimated exposure for each exposure scenario and product. When the resulting MOE is greater than 100, the Agency's level of concern (LOC) is not exceeded and there is reasonable certainty of no harm to human health. For purposes of defining the level of concern, the uncertainties are associated with extrapolation of animal data to humans (10x) and intraspecies variation (10x). An additional uncertainty factor was not retained for the sensitivity of infants and children in this case because the endpoint is based on toxicity observed in offspring in the absence of parental toxicity in a reproduction study.

Based on the available information and calculations in the exposure assessment, all except one of the estimates exceeded the Agency's level of concern (Margins of Exposures < 100). Calculated MOEs ranged from 88 to 1303. This includes combined exposures for the same use pattern (i.e. dermal and incidental oral exposure). The scenario that resulted in an MOE of 88 is the only scenario which was calculated to be less than 100. This scenario is the result of a combined exposure estimate and is not a realistic estimate of risk due to the assumptions used which tend to exaggerate potential exposure (i.e. 100% dermal absorption and maximum transfer coefficients).

The pet treatment, carpet and surface treatment, and fogger products all contain multiple active ingredients. The exposure assessment only addressed the Linalool component of

those products containing additional active ingredients. The other active ingredients will be addressed during their subsequent registration review.

6. Human Health Risk Characterization: Based on the above human hazard assessment and the results of the exposure assessment in which exposure scenarios did not exceed the Agency's level of concern, anticipated risk is not likely to result in unreasonable effects to human health when products containing Linalool are used in accordance with the label.

C. Environmental Assessment

1. Nontarget Organisms and Environmental Fate Testing Requirements: As per 40 CFR Part 158.2060, the registrant of Technical Linalool submitted or cited required nontarget organisms and environmental fate studies to support the registration of Technical Linalool. Information summarized below and included in Table 3 was obtained from the following: Biopesticides and Pollution Prevention Division (BPPD) Data Evaluation Record (DER) from Russell S. Jones dated 11/4/98; Ecological Effects Branch Data Evaluation Report from Daniel Rieder dated 3/14/85.

a) Avian Testing TIER I: Avian acute toxicity testing is not required for biopesticide products with indoor uses only. However, the registrant did cite or submit acute dietary toxicity data (for the Bobwhite Quail). The Agency determined that the data were acceptable to support a $LC_{50} > 5620$ ppm which is considered practically non-toxic.

For outdoor uses, a waiver request from the requirement of a guideline study for avian testing was granted because there is no direct exposure of Linalool to birds, aquatic organisms, and non-target plant and insects. Linalool is used outdoors in fragrance generators or candles to inhibit mosquitoes and in shampoo products to control fleas and ticks on pets. The Agency determined that there would be no direct exposure to birds, aquatic organisms, and non-target plants and insects from the mosquito inhibitor products as the products are contained within a screened device or a candle. For both pet shampoos and mosquito inhibitors, environmental exposure occurs entirely via volatilization into the atmosphere, or by direct contact with a pet treated with a Linalool-containing shampoo. Linalool is rapidly diluted by the atmosphere as it diffuses away from its point sources in fragrance generators and candles, and on animals (as a component of pet treatment products).

b) Aquatic Organism Testing (TIER I): Aquatic organism testing is not required for indoor use only biopesticides. However, the registrant did cite or submit fresh water fish (Rainbow Trout and Bluegill) studies and aquatic organism testing studies. The Agency determined that the data were acceptable to

support an $LC_{50} > 28.8$ ppm for Rainbow Trout, a LC_{50} 36.8 ppm for Bluegill, and a LC_{50} 36.7ppm for aquatic invertebrates. The above LC_{50} s for fresh water fish and aquatic organisms are considered practically non-toxic and slightly toxic respectively.

For outdoor uses of Linalool, a waiver was requested and granted for aquatic organism testing based on rationale stated above for the waiver sought and granted for avian testing.

c) Non-Target Plant, Insect, Environmental Fate, Aquatic Fauna and Terrestrial Wildlife Testing (TIER I, II & III): Testing is not required for indoor use only products.

For outdoor uses of Linalool, testing was not required or waivers granted based on the rationale stated above for the waiver sought and granted for avian testing.

Table 3: Nontarget Organisms and Environmental Fate Testing Requirements				
Data Requirement 40 CFR Part 2060	Guideline	MRID#	Classification	Results Summary
Avian Testing (TIER I)				
Avian Oral	850.2100	NA	NR For Indoor Uses Waiver Granted for Outdoor Use	NA
Avian Dietary	880.2200	N/A	NR for Indoor Use Waiver Granted for Outdoor Use	An $LC_{50} > 5620$ was assigned based on information cited in public literature.
Aquatic Organism Testing (TIER I)				
Fresh Water Fish Acute Toxicity	850 1075	N/A	NR for Indoor Uses Waiver Granted for Outdoor Use	The following LC_{50} s were assigned based on information cited in the public literature. Rainbow Trout: >28.8 ppm; Bluegill: 36.8 ppm;

Table 3: Nontarget Organisms and Environmental Fate Testing Requirements				
Data Requirement 40 CFR Part 2060	Guideline	MRID#	Classification	Results Summary
Fresh Water Aquatic Invertebrate Acute Toxicity	850.1010	NA	NR for Indoor Uses Waiver Granted for Outdoor Use	An LC ₅₀ of 36.7 was assigned based on information cited in public literature.
Nontarget Plant (TIER I & II) & Insect Testing (TIER I)				
Terrestrial Plant Toxicity, Seedling emergence	850.4100		NR for Indoor Uses Waiver Granted for Outdoor Use	NA
Terrestrial Plant Toxicity, Vegetative vigor	850.4150		NR for Indoor Uses Waiver Granted for Outdoor Use	NA
Non-Target Insect Testing	880.4350		NR for Indoor Uses Waiver Granted for Outdoor Use	NA
All Environmental Fate Testing (TIER II) Testing Not Required				
Aquatic Fauna Chronic, Life Cycle, and Field Studies (TIER III) Testing Not Required				

2. Endangered Species Assessment (ESA): The following assessment is cited from the Biopesticides and Pollution Prevention Division (BPPD) Memorandum from Russell Jones dated June 26, 2008.

Linalool is intended for use indoors to control pests and as an outdoor insect inhibitor. Outdoor uses of Linalool only affect (inhibit) biting insects; other non-target insects are unaffected. When used indoors, it is applied directly to dogs and cats (as shampoos, dips and sprays) and is used as an indoor carpet and surface treatment (as sprays, powders and foggers) to control fleas, mites, spiders and ticks. Linalool is used outdoors in fragrance generators and candles to inhibit mosquitoes.

Outdoor exposure also may occur when pets treated with Linalool-containing shampoos are permitted to be outdoors. There is no exposure to non-target organisms resulting from strictly indoor uses. For outdoor uses, environmental exposure occurs entirely via volatilization into the atmosphere, or by direct contact with a pet treated with a Linalool-containing shampoo. Linalool is rapidly diluted by the atmosphere as it diffuses away from its point sources in fragrance generators and candles, and on animals (as a component of pet treatment products).

Due to the volatility of Linalool and its rapid dilution in the atmosphere, outdoor uses preclude any residue accumulation in terrestrial and aquatic environments. Direct exposure to birds, fish, aquatic invertebrates or plants via direct contact with a pet treated with a Linalool-containing shampoo is expected to be extremely low. Outdoor uses of Linalool only affect (inhibit) biting insects; other non-target insects are unaffected.

Linalool was approved by FDA as a direct food additive and was given Generally Recognized As Safe (GRAS) status for use as a flavor in both human and animal food under the following FDA regulations: (i) 21 CFR 172.515, Food Additives Permitted for Direct Addition to Food for Human Consumption; (ii) 21 CFR 182.60, Substances Generally Recognized As Safe, Food for Human Consumption Synthetic Flavoring Substances and Adjutants; (iii) and 21 CFR 582.60, Substances Generally Recognized as Safe, Animal Drugs, Feeds, and Related Products. The GRAS status for Linalool use in human food was approved in 1965 (see MRID 44597401). The active ingredient is used in many consumer products including soaps, detergents, and perfumes.

Based on this screening level assessment, EPA has determined that there will be No Effects (NE) of Linalool on threatened or endangered terrestrial or aquatic species as listed by the U.S. Fish and Wildlife Service (USFWS) when products containing this active ingredient are used in accordance with approved labeling.

3. Ecological Risk Characterization: Based on the review of the above stated non-target organisms and environmental fate studies, and the Endangered Species Assessment, EPA has determined that anticipated risk is not likely to result in unreasonable risk to non-target organisms or the environment when products containing Linalool are used in accordance with the label.

D. Product Performance (Efficacy):

Product performance data must be developed for all pesticides. However, the Agency typically does not require applicants to submit such efficacy data unless the pesticide product bears a claim to control public health pests.

There are currently two registered products containing Linalool with label claims to inhibit mosquitoes; Biosensory's Mosquito Cognito, EPA Reg. No. 70909-2, and Biosenory's Conceal Candle, EPA Reg. No. 70909-5. Since the mosquito is considered a public health pest, the registrant was required to submit efficacy studies for Agency review.

1. Mosquito Cognito: Two field studies were conducted in Florida to satisfy efficacy data requirements. Each study showed that Linalool was only partially effective in reducing mosquito activity. The Agency determined that the studies did not support the product label claims. Pending the submission and review of acceptable studies, the Agency required the registrant to remove labeling statements to the effect that Mosquito Cognito "blocks" mosquitoes. The registrant complied and the label now states that Mosquito Cognito "inhibits" mosquitoes.

2. Conceal Candle: This product was issued a Conditional Registration on December 21, 2004 pending the submission and acceptance of product performance and storage and stability data. To date, there are remaining deficiencies in regard to product performance that have not been satisfactorily addressed by the registrant. However, in spite of these deficiencies, the Agency believes that Linalool has proven to be efficacious and remaining concerns are based on whether the specific mode of action is consistent with labeling and marketing claims. The registrant has been working with the Agency to address these conditions of registration through the normal product registration regulatory process.

E. Incidents:

The following is information summarized from the Biopesticides and Pollution Prevention Division (BPPD) Memorandum from Roger Gardner, January 28, 2007. Federal law requires registrants of pesticides to inform EPA about any harmful effects of their products. The National Pesticides Information Center (NPIC) compiles an incident database which is often used by EPA to monitor and analyze reported pesticide incidents. NPIC data indicated a total of 281 incidents associated with products containing Linalool over a 14 year period (approximately 20 per year). Of the reported incidents, there were 199 reports of incidents involving humans and 82 involving domestic animals.

There were no incidents reported for products containing Linalool as the sole active ingredient nor was there any evidence from the reports that there were misuses of products containing Linalool. The products involved in the reported incidents all contained multiple active ingredients including insect growth regulators, pyrethrins, prallethrin, permethrin, and piperonyl butoxide. The signs of toxicity were mostly dermal and eye irritation that are human health hazards mentioned in the precautionary labeling for products involved.

Based on the fact that no incidents were reported for single a.i. products containing only Linalool, and the low toxicity of Linalool during testing, the Agency determined that incident reports did not indicate any specifically Linalool-related causes.

F. Environmental Justice

EPA seeks to achieve environmental justice - the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income - in the development, implementation, and enforcement of environmental laws, regulations, and policies. At this time EPA does not believe that use of pesticide products containing Linalool will cause harm or a disproportionate impact on at-risk communities.

To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to pesticide products containing Linalool, compared to the general population. Please comment if you are aware of any sub-populations who may have higher exposure than the general population. The Agency will consider public comments and any additional information submitted in response to this docket to determine the need for new data and/or a new risk assessment.

For additional information regarding environmental justice issues, please visit EPA's website at: <http://www.epa.gov/compliance/environmentaljustice/index.html>.

IV. RISK MANAGEMENT AND REGISTRATION REVIEW DECISIONS

A. Registration Review

FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandated the continuous review of existing pesticides. All pesticides distributed or sold in the United States must generally be registered by EPA, based on scientific data showing that they will not cause unreasonable risks to human health, workers, or the environment when used as directed on product labeling. The Registration Review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the new registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at: http://www.epa.gov/oppsrrd1/registration_review/.

Pursuant to 40 CFR Sec. 155.50, the Agency formally initiated Registration Review for Linalool with the following timeline:

- April 11, 2007 – publication of a preliminary work (PWP) in the initial docket for Linalool (EPA-HQ-OPP-2006-0356).
- April 11, 2007 through June 11, 2007. During the 60 day comment period, the Agency received comments from the Physicians Committee for Responsible Medicine (PCRM) and from Tri TAC, a technical advisory committee for publicly owned treatment works (POTWs). *See below for more details regarding the submitted comments and the Agency's response(s).*
- August 23, 2007 – Issuance of a Final Work Plan addressing the public comments and stating that the most recent exposure and risk assessments still supported the registration pesticide products containing Linalool and met the requirements of registration review under 40 CFR Sec. 155.50.
- Projected April 2007 – Issuance of a Proposed Final Decision for public comment
- Projected June 2007 – Issuance of Final Decision

EPA's is issuing a proposed Registration Review Decision for Linalool pursuant to 40 CFR Sections 155.57 and 155.58. A Registration Review Decision is the Agency's determination that a pesticide meets, or continues to meet the standard for registration in FIFRA.

The Agency's Final Decision is that no additional data are required at this time to support the continued registration of Linalool. The Agency has considered Linalool in light of the standard for registration and safety factors in FIFRA and FFDCA as amended by FQPA. EPA has found that there are not likely to be any unreasonable adverse effects to the U.S. population in general, and to infants and children in particular, or to non-target organisms, from the use of products containing Linalool when currently required label instructions are followed. The Final Decision Document for Linalool is not expected to require further data requirements for currently registered pesticide products containing Linalool. However, if additional information is submitted that warrants further risk assessment, the Agency will then conduct any necessary risk assessment(s) prior to issuing the Final Registration Review Decision.

The data and information evaluated to support Linalool (case 6058) as published in the PWP (04/11/2007) continue to support this pesticide registration as summarized herein and in the Registration Review Final Decision which is available on [http://www.epa.gov/oppsrrd1/registration review/ review/](http://www.epa.gov/oppsrrd1/registration%20review/review/).

B. Regulatory Position

- 1. Unconditional and Conditional Registrations:** The data requirements are fulfilled for the currently registered products. Data requirements for conditionally registered products are outlined in section III D.

In order to register new products (or amend labeling of existing products) with new sites or application methods which are likely to increase environmental or human health exposure over the currently registered sites on the label, the

registrant must consult with the Agency about the need for additional data, or sound scientific rationales to waive data requirements.

2. **Tolerances for Food Uses and /or Exemption:** This section is not applicable as there are no food uses or tolerances for Linalool.
3. **CODEX Harmonization:** There are no Codex harmonization considerations since there is no Codex Maximum Residue Limits set for food use of Linalool based on the rational explained in 2 above.
4. **Risk Mitigation:** There is minimal or negligible potential risk human health or to non-target organisms (plants and wildlife), and to ground and surface water contamination through the proposed use of products containing Linalool.

C. Labeling

The labels and labeling of all products must comply with EPA's current regulations and requirements as specified in 40 CFR Part 156.10 and other applicable notices, such as, and including the Worker Protection Standard (WPS) labeling. Linalool products are not subject to the Worker Protection Standard.

Labels for registered products containing the active ingredient Linalool are available at <http://oaspub.epa.gov/pestlabl/ppls.home>. The PC code for this active ingredient is 128838.

V. ACTIONS REQUIRED BY REGISTRANTS

Registrants with conditional registrations must provide acceptable data to satisfy the conditions of their registrations.

Reports of incidents of adverse effects to humans or domestic animals are required under FIFRA, Section 6(a)(2) and incidents of hypersensitivity under 40 CFR Part 158.690(c), data requirement reference number 152-16.

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2. Joint FAO/WHO Expert Committee on Food Additives Meeting Summary and Conclusions (2003)
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